PCT / IN 04/ 00342

INTELLECTUAL PROPERTY **INDIA**
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सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 05/11/2003 in respect of Patent Application No.1164/MUM/2003 of M/S. LYKA LABS LIMITED, 77, Nehru Road, Vile Parle (East), Mumbai – 400 099, Maharashtrta, India, An Indian Company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

Dated this 18th day of January 2005.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
[See section 5(2), 7, 54 and 135; rule 39]

1. We,

   (a) M/S. LYKA LABS LIMITED

   (b) 77, Nehru Road, Vile Parle (East), Mumbai – 400 099, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled **"A novel drug delivery system for proton pump inhibitors and process thereof"**

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) **Bajaj, Mannalal Ramgopal**
   (b) Lyka Labs Limited
   77, Nehru Road, Vile Parle (East)
   Mumbai 400 099
   Maharashtra, India
   (c) Indian National

   1164
   5439

   (a) Samant, Rajan Shantaram
   (b) Lyka Labs Limited
   77, Nehru Road, Vile Parle (East),
   Mumbai 400 099
   Maharashtra, India
   (c) Indian National

1164/mum/2003

5/11/2003

Received Rs. 3500/- in Cash
vide M.O./P.O. dt. 5/11/03
vide Entry No. 5439 in the
Register of Valuables, Bombay.
5-11-03

(a) **Shah, Bharat Babulal.**
(b) Lyka Labs Limited.
77, Nehru Road, Vile Parle (East),
Mumbai 400 099
Maharashtra, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Bajaj, Mannalal Ramgopal)

(Samant, Rajan Shantaram)

(Shah, Bharat Babulal)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) Fee Rs.3000/- in cheque bearing No. 623901 dated 4th Nov 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 4th day of Nov 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road
Kandivli (East), Mumbai – 400 101

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
[See section 10; rule 13]

"A novel drug delivery system for proton pump inhibitors and process thereof"

(a) **LYKA LABS LIMITED.**

(b) 77, Nehru Road, Vile Parle (East), Mumbai – 400 099, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

The following specification particularly describes the nature of the invention:

A novel drug delivery system for proton pump inhibitors and process thereof

Technical Field of the Invention:

This invention relates to a stabilized dosage form for Proton Pump Inhibitors (PPIs). More particularly, this invention discloses a novel, stable, pharmaceutically acceptable, regulatory compliant injectable form of Rabeprazole in lyophilized form. This invention also relates to a process for lyophilization of Rabeprazole.

Background and Prior Art:

Proton pump inhibitors (PPIs) form the emerging anti-ulcer compounds and have already overtaken H2 antagonists like Ranitidine. PPIs are now the drugs of choice for stomach and duodenal ulcers. They are also effectively used to relieve symptoms of esophagistis and acute gastro-esophageal efflux. PPIs are also used to alleviate *Helicobacter pylori* infection which is considered to be the root cause of stomach ulcers. PPI's block the production of stomach acids by inhibiting a system in the stomach known as proton pump, also referred to as hydrogen –potassium adenosine triphosphate enzyme system.

Omeprazole (also esomeprazole), Lansoprazole, Pantoprazole and Rabeprazole are the leading commonly used proton pump inhibitors (PPIs). Owing to the close similarity between these PPIs, the formulations and dosage forms can be similarly formulated for all of the group of compounds based on a process developed for any one of the group of PPIs.

Rabeprazole (marketed as Aciphex in USA and other countries) is available only in tablet form or as sustained release tablets in NDDS.

Rabeprazole has been administered by employing any suitable route of administration such as rectal, transdermal and like forms with effective dosage of active ingredient, however oral administration has hitherto been the preferred route. Reported oral dosage forms are tablets, troches, dispersions, suspensions, solutions, capsules and the like.

World Patent application WO9601624 describes a pharmaceutical formulation in the dosage form of multiple unit tablets which contains active ingredient, an acid labile H+K+ATPase inhibitor like Rabeprazole, or alkaline salts thereof.

Oral dosage forms for Rabeprazole are also disclosed in US patent number 5,035,899 and World Patent application WO97/12580 and WO97/25030.

Compositions of Rabeprazole suitable for rectal administration are described in European Patent application, 645140.

Further, the injections for PPI's have recently been developed. Japanese Patent unexamined Publication no. JP167587/1984 describes the process for preparation of injection of Omeprazole. The process comprises dissolving sodium salt of Omeprazole in sterilized water, filtering and lyophilizing the solution to give lyophilized product. This lyophilized product is dissolved in a mixture of polyethylene glycol 400 for injection, sodium dihydrogen phosphate and sterilized water.

For Lansoprazole the lyophilized injection is prepared by dissolving lyophilized product of Lansoprazole in a mixture of acid and at least one of ethanol, propylene glycol and polyethylene glycol as described in Japanese unexamined patent no. JP138213/1990.

Freeze dried injectable formulation of Pantoprazole is described in World Patent application WO0241919. Lyophilization of the aqueous solutions of Pantoprazole, ethylenediamine tetraacetic acid and/or a suitable salt thereof, and sodium hydroxide and/or sodium carbonate are disclosed

Freeze dried formulations for Omeprazole and Lansoprazole, as described in World Patent application WO9402141, comprises the benzimidazole compounds or their salts to which are added an aqueous solvent wherein the pH is not less than 9.5 and not more than 11.5.

However, there is no formulation or delivery system for Rabeprazole in particular, in injectable form. We have developed lyophilized, stable injectable dosage form of Rabeprazole, the process of which could also be applied for other PPIs like, Omeprazole, Lansoprazole, and Pantoprazole etc.

Objective of the Invention:

Our objective of this invention is to make available commercially stabilized pharmaceutically acceptable dosage form of proton pump inhibitors in general and Rabeprazole in particular as lyophilized (freeze dried) injection in stabilized dosage form.

Summary of the Invention:

A stabilized lyophilized dosage form of Rabeprazole is formulated which is stable, pharmaceutically acceptable and regulatory compliant. This novel lyophilization process described herein and the lyophilized stable injectable form of Rabeprazole are also applicable to other Proton Pump Inhibitors like Omeprazole, Lansoprazole and Pantoprazole etc.

Detailed Description:

According to the present invention, an injection of Rabeprazole compound or its sodium salt can be prepared by dissolving the same in water for injection, along with Sodium Metabisulphite or strong alkaline compounds such as Sodium Hydroxide. This solution will also contain Mannitol. The solution is filtered and filled in previously sterilized vials.

Rabeprazole Sodium for injection (10mg/vial) is prepared by dissolving Sodium Metabisulfite and Mannitol in pre-cooled Water for Injection. Rabeprazole sodium is added to this solution and the volume is adjusted with Water for Injection. The above solution is filtered aseptically through 0.22μ filter paper and 2.0 ml of filtered solution is filled in previously sterilized vial. After partial bunging, the vials are loaded into lyophilyser.

Rabeprazole Sodium for injection (20mg/vial) is prepared by dissolving Sodium hydroxide in Water for Injection to make 0.01M solution to adjust the pH above 12.0. Mannitol and Rabeprazole sodium are added to the above solution, maintaining the pH the same and making up the volume. The above solution is filtered aseptically through 0.22μ filter paper and 2.0 ml of filtered solution is filled in previously sterilized vials. After partial bunging, the vials are loaded into lyophilyser.

The present invention will now be further illustrated by the following examples.

Example 1

Approximately 250ml of pre-cooled Water for Injection (WFI) is taken into a flask. 40mg of Sodium Metabisulfite and 4.5gm of Mannitol is dissolved in it. Then, 1.676gm of Rabeprazole sodium is added and dissolved. The volume is adjusted to 300ml with Water for Injection. The above solution is filtered aseptically through 0.22μ filter paper and 2.0 ml of filtered solution is filled in previously sterilized vial. After partial bunging, the vials are loaded into lyophilyser. The resulting formulation contained the following components in the following amounts.

Rabeprazole Sodium for injection 10mg/vial

Ingredients	Specification	Qty per vial	Qty per 300ml (150 vials)	Qty per 20,000 vials
Rabeprazole Sodium eq. to Rabeprazole	IH	10 mg	1.676 gm	223.44 gm
Mannitol	IP	30 mg	4.5 gm	600 gm
Sodium Metabisulfite	IP	0.26 mg	40 mg	5.2 gm
Water for Injection before lyophilization qs.	IP	2.0 ml	300 ml	40 lts

IH - Inhouse Specifications

IP - Indian Pharmacopoeia

Example 2

Sodium hydroxide is dissolved in Water for Injection to make 300ml of 0.01M solution. To 280ml of this solution add Mannitol (4.5gm) and Rabeprazole sodium (3.352gm), maintaining the pH above 12 and make up the volume. The above solution is filtered aseptically through 0.22μ filter paper and 2.0 ml of filtered solution is filled in previously sterilized vial. After partial bunging, the vials are loaded into lyophilyser. The resulting formulation contained the following components in the following amounts.

Rabeprazole Sodium for injection 20mg/vial

Ingredients	Specification	Qty per vial	Qty per 300ml (150 vials)	Qty per 20,000 vials
Rabeprazole Sodium eq to Rabeprazole	IH	20 mg	3.352 gm	447 gm
Mannitol	IP	30 mg	4.5 gm	600 gm
Sodium hydroxide	IP	0.8 mg	120 mg	16 gm
Water for Injection before lyophilization qs.	IP	2.0 ml	300 ml	40 lts

IH - Inhouse Specifications

IP - Indian Pharmacopoeia

While the present invention is described above in connection with preferred or illustrative embodiments, these embodiments are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its spirit and scope, as defined by the appended claims.

The examples mentioned above for Rabeprazole and the process for lyophilization, the conditions including pH and pharmaceutically acceptable inactive ingredients used therein are also applicable for other Proton Pump Inhibitors and lyophilized dosage forms thereof.

Dated this the 4th day of Nov 2003

Dr. Gopakumar G. Nair
Agent for the Applicant

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